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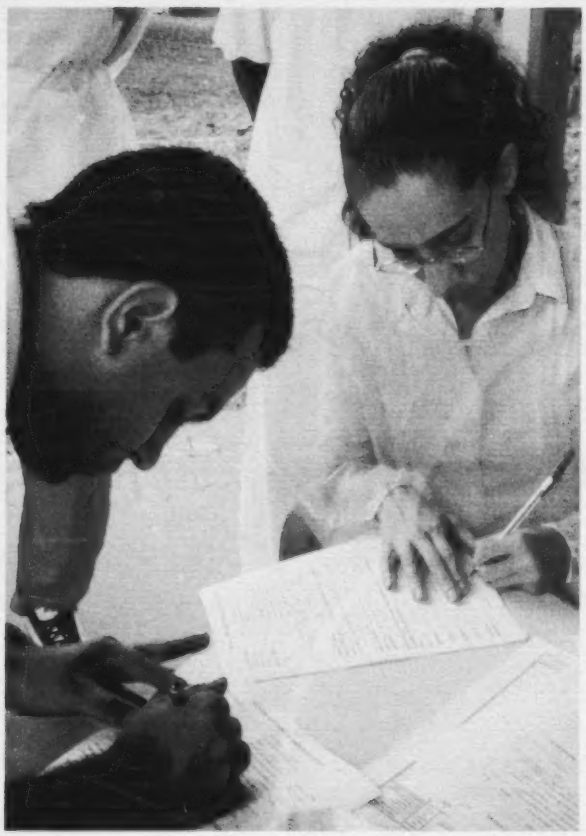
CCDR

CANADA COMMUNICABLE DISEASE REPORT

SCIENTIFIC WRITING



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CCDR
CANADA COMMUNICABLE DISEASE REPORT

The *Canada Communicable Disease Report* (CCDR) is a bilingual, peer-reviewed, open-access, online scientific journal published by the Public Health Agency of Canada (PHAC). It provides timely, authoritative and practical information on infectious diseases to clinicians, public-health professionals, and policy-makers to inform policy, program development and practice.

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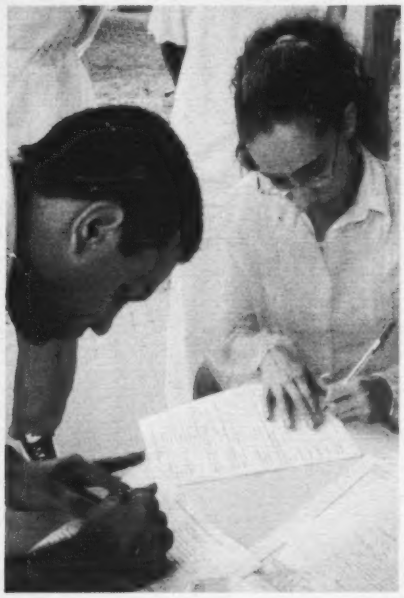

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A reporting guide for implementation science articles

Correspondence: ccdr-rmtc@phac-aspc.gc.ca

Suggested citation: A reporting guide for implementation science articles. Can Comm Dis Rep 2016;42:175-6.

Many health and public health practitioners are interested in "what's new"— how evidence can be applied to practice and what works. Implementation science has been described as the scientific study of methods to promote the uptake of research findings into routine healthcare in clinical, organizational or policy contexts (1). In the *Canada Communicable Disease Report* (CCDR), this can include any process, procedure, policy or program designed to decrease the human impact of an infectious disease.

There is often a gap between the positive findings of an experimental study and outcomes in practice. This is in part because effective implementation is difficult. It requires significant knowledge, skills and effort to assess, plan, adapt, deliver, monitor and evaluate an intervention. Implementation science aims to understand and decrease the gap between evidence and practice. Excellent manuals have been developed, such as one by the RAND Corporation (2) and a variety of theoretical models have been proposed and are being tested (3,4). These have revealed that multiple factors are at play. For example, a systematic review identified that evidence–based clinical practice guidelines were almost three times more likely to be adopted if they were supported by a facilitator who used strategies such as audit and feedback, as well as interactive consensus building and goal setting (5). Clearly, implementation is both an art and a science.

Because there has been little guidance available to date for reporting implementation science articles, the CCDR has developed a 20-item checklist based on the literature and best practice in scientific communications. This checklist identifies the need to describe what is being implemented and why, who is being targeted and where, how the implementation was done, what the outcomes were, what lessons were learned and potential next steps (**Table 1**).

An implementation science paper is usually 1,500 to 2,000 words in length. As with all submissions, check CCDR's *Information for authors*, published at the beginning of a new volume in January of each year for general manuscript preparation and submission requirements (6).

Table 1: Checklist for implementation science papers

Reporting item	No.	Description
Title/Abstract		
Title	1	Compose a title that includes the population, condition or primary issue addressed in the study.
Abstract	2	Provide a 200 to 250-word abstract using the following sub-headings: Background, Objective, Intervention, Outcomes and Conclusion.
Introduction		
Issue identification	3	Identify the topic of the study and why it is important.
What is known to date	4	Provide a summary of the literature relating to the topic and identify any existing gaps.
Rationale for study	5	Identify the rationale for the implementation study.
Objective	6	State the objective of the intervention.
Intervention		
Setting/ participants	7	Describe the setting and population used for the implementation study, and the rationale for both.
Ethics review if indicated	8	For studies involving human participants, include a statement detailing ethical approval and consent.
Intervention	9	Describe the intervention and how it was carried out. If applicable, state who offered the intervention, how participants were enlisted, what efforts were made to adapt the intervention to local needs, enabling factors and any training given.
Outcome measures	10	Describe how the intervention was assessed. This may include descriptive statistics about the participants (or target population) as well as primary and secondary outcome measures. If appropriate, describe the analyses conducted to examine sub-groups, interactions and confounding factors.
Outcomes		
Setting/ participants	11	Present the findings in enough detail to give a sense of the participants or target population, time and place.
Primary outcomes	12	Present the primary outcome measure(s).

Secondary outcomes	13	Provide any secondary outcome measures, sub-group analysis, interactions or confounding factors if applicable.
Intervention experience	14	Describe any insights that arose as a result of implementing the intervention.
Discussion		
Summary of key findings	15	Summarize and interpret the key findings of the intervention and its implementation.
Comparisons	16	Compare the results of the intervention with previous findings (such as how the intervention was implemented in different populations or settings).
Strengths and limitations	17	Identify the strengths and limitations of the intervention and its implementation.
Implications and next steps	18	Consider implications, next steps or further areas of inquiry (such as a more in-depth evaluation, assessment in other contexts, potential for scale-up and sustainability).
Conclusion	19	Ensure the conclusion integrates the key findings and addresses the objective of the study.
Tables or figures		
Illustrating key findings	20	When appropriate, include an illustrative diagram or table summarizing key points.

Abbreviation: No., Number

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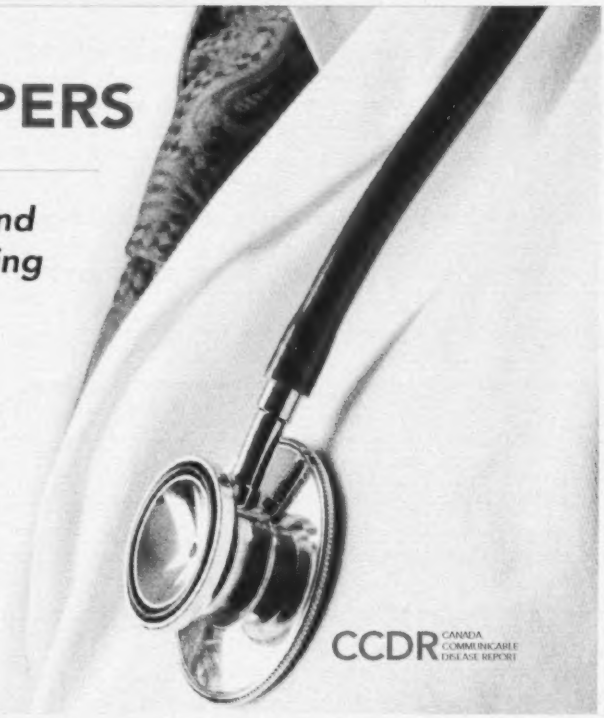

A reporting guide for qualitative studies

Correspondence: ccdr-rmtc@phac-aspc.gc.ca

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Qualitative studies provide insight into complex phenomena. Unlike measurement-based studies which typically quantify what happens under experimental conditions, qualitative studies often help explain behaviours or perceptions under actual circumstances. Qualitative studies in the field of communicable diseases can be used to provide insights into why people choose high-risk behaviours and to identify factors that influence their decisions. For example, a qualitative study may address why healthcare practitioners do not practice adequate hand hygiene and whether patients might help by reminding them to do so. The results can be surprising. For example, a recent study identified that inpatients in one hospital who were most dissatisfied with the care they received were also the least likely to ask healthcare professionals if they had washed their hands (1). Furthermore, the study identified that the decision not to pose this question was linked to patient awareness that staff satisfaction was low.

Qualitative research analyzes data from direct field observations, in-depth, open-ended interviews and written documents. Inductive analyses yield patterns and themes that generate hypotheses and offer a basis for future research. Although qualitative studies do not create generalizable evidence, well-reported studies provide enough information for readers to assess the applicability or transferability of findings to their own context (2).

There are a variety of checklists on how to report qualitative studies (3-6). The *Canada Communicable Disease Report* (CCDR) has developed a 24-item checklist that synthesizes these including the COREQ checklist noted on the EQUATOR Network (6). The CCDR checklist identifies the importance of describing how data was gathered and summarized, what trends were determined, exploring corroborative findings, offering alternative explanations and identifying possible next steps (**Table 1**).

Reports of qualitative studies are usually around 2,500 words in length—excluding the abstract, tables and references. As with all submissions, check CCDR's *Information for authors*, published at the beginning of each volume in January of each year for general manuscript preparation and submission requirements (7).

Table 1: Checklist for qualitative studies

Reporting item	No.	Description
Title/Abstract		
Title	1	Compose a title that includes the term "qualitative", the population, condition, place and time.
Abstract	2	Use a structured abstract format with the following section headings: Background, Objective, Methods, Findings and Conclusion.
Introduction		
Issue identification	3	Identify the topic of the study and why it is important.
Review of literature	4	Provide a summary of the literature relating to the topic and what gaps there may be.
Rationale for study	5	Identify the rationale for the study. The rationale for the use of qualitative methods can be noted here or in the methods section.
Objective	6	Clearly articulate the objective of the study.
Ethics approval	7	Note here or in the methods section whether ethics board review was indicated, and if it was, where review and approval was obtained.
Method		
Setting	8	Describe the setting of the study and the relationship of the researcher to study participants (if any).
Approach	9	Identify the qualitative methods (e.g., interviews, participant observation) used in the study, any theoretical underpinnings if appropriate (e.g., grounded theory) and the rationale for their use.
Populations	10	Describe the groups from which people were invited to participate in the study.
Sampling	11	Identify the sampling strategies for the study (e.g., theoretical sampling, snowball technique).
Data collection	12	Describe how data collection tools were developed (e.g., pilot testing of interview guides) and how the data were recorded (e.g., audio, audiovisual or field notes).

Analysis	13	Identify how the data were managed and analyzed, including any software system used, and how information was assessed for credibility and transferability (e.g., member checking, inter-observer reliability and triangulation).
Synthesis	14	Describe how the findings were synthesized (e.g., what were the principles and choices informing the recognition of patterns and formation of categories? How were major and minor themes developed?).
Findings		
Sample	15	Identify the total sample size and non-participation rate.
Population, time and place	16	Present the findings in context, i.e., with enough background and contextual detail to give a sense of the population, time and place (e.g., through appropriate use of quotes).
Analysis	17	Present an analysis that is credible and compelling (i.e., themes flow logically from the findings; relations between data and theoretical models and perspectives are described; interpretations are insightful).
Comparisons	18	Explore corroborative findings (e.g., triangulation) and consider contradictory or diverse opinions (e.g., negative cases).
Synthesis	19	Present findings in such a way that they clearly address the research objective.
Discussion		
Summary of key findings	20	Summarize key findings and indicate how the findings are relevant to the objective of the study.
Strengths and weaknesses	21	Identify the strengths and weaknesses of the study and consider alternative explanations for the findings when appropriate.
Transferability	22	Explore the implications of the study considering the applicability or transferability of the findings.
Next steps	23	Propose next steps or further areas of inquiry.
Conclusion	24	Ensure the conclusion integrates the data and analysis and addresses the objective of the study.

Abbreviation: No., Number

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EDITORIAL POLICY

A reporting guide for overviews

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Suggested citation: A reporting guide for overviews. Can Comm Dis Rep 2016;42:179-80.

Overviews are useful to explore a new area, summarize the state of evidence on a broad topic, and provide insight into the progression of a body of research. Because evidence in clinical and public health evolves rapidly, an expert summary and assessment can be extremely valuable. For example, what are the challenges in eliminating pediatric HIV infection (1)? Or what is the current evidence regarding prion disease? Prior diseases were once thought to be extremely rare, but have now been linked to a much broader group of protein-misfolding disorders that may be more common than previously thought (2). An overview by an expert in the field can provide a useful introduction to emerging issues as well as a framework to better understand subsequent developments (3).

Overviews are not underdeveloped systematic reviews. Systematic reviews are best for specific topics (4). For example, a systematic review is often used to analyze the evidence on the effectiveness of a specific drug for a specific condition in a specific population. Overviews are best for general topics. A systematic review is research that puts evidence under a microscope; an overview is an evidence-based expert opinion that scans a body of evidence with binoculars.

The potential weakness of an overview is bias. Readers need to be assured that the evidence summarized is fair and accurate, and not inappropriately selective. A multi-database literature search with the support of a research librarian can help address this (5) as will a transparent analysis. The goal of an overview is not to provide the highest level of evidence, but rather to summarize, analyze and edify.

Because we are unaware of any reporting guidelines for an overview paper, the *Canada Communicable Disease Report* (CCDR) has developed a 16-item checklist based on the literature and best practice in scientific communications. This checklist identifies the need to address a topic in a way that is logical, balanced and insightful, including the consideration of contradictory evidence, strengths and limitations, and potential next steps (**Table 1**).

An overview is generally 1,500 to 2,000 words in length. As with all submissions, check CCDR's *Information for authors*, published at the beginning of each volume in January of each year for general manuscript preparation and submission requirements (6).

Table 1: Checklist for overview papers

Reporting item	No.	Description
Title/Abstract		
Title	1	Compose a title that includes the population, condition or primary issue addressed in the overview.
Abstract	2	Provide a 200 to 250-word abstract that identifies the issue, why it is important, the objective of the overview, key points and a conclusion.
Introduction		
Issue identification	3	Identify the topic of the study and why it is important.
Rationale for study	4	Identify the rationale for providing an overview.
Objective	5	Clearly articulate the objective of the overview.
Scope		
Setting/population	6	Describe the setting or populations identified for the overview.
Approach	7	Identify any decision points about what to include or not include in the overview and the rationale.
Literature search	8	Identify any literature searches conducted to address potential bias.
Key findings		
Population, time and place	9	When applicable, present the findings in enough detail to provide a sense of the population, time and place.
Logical, balanced and insightful analysis	10	Present an analysis that demonstrates how the overview addresses the stated objective; is logical, includes countervailing evidence when indicated to provide a balanced view, and provides an expert interpretation of the literature.
Supported with references	11	Support assertions and facts with appropriate references.
Discussion		
Summary of key findings	12	Summarize key findings and indicate how the findings are relevant to the objective of the study.
Comparative analysis	13	Explore corroborative findings and consider contradictory evidence (if available).
Strengths and limitations	14	Identify the strengths and limitations of the state of knowledge for the overview topic.
Next steps	15	Propose next steps or further areas for inquiry.
Conclusion	16	Ensure the conclusion integrates the key findings and addresses the objective of the study.

Abbreviation: No., Number

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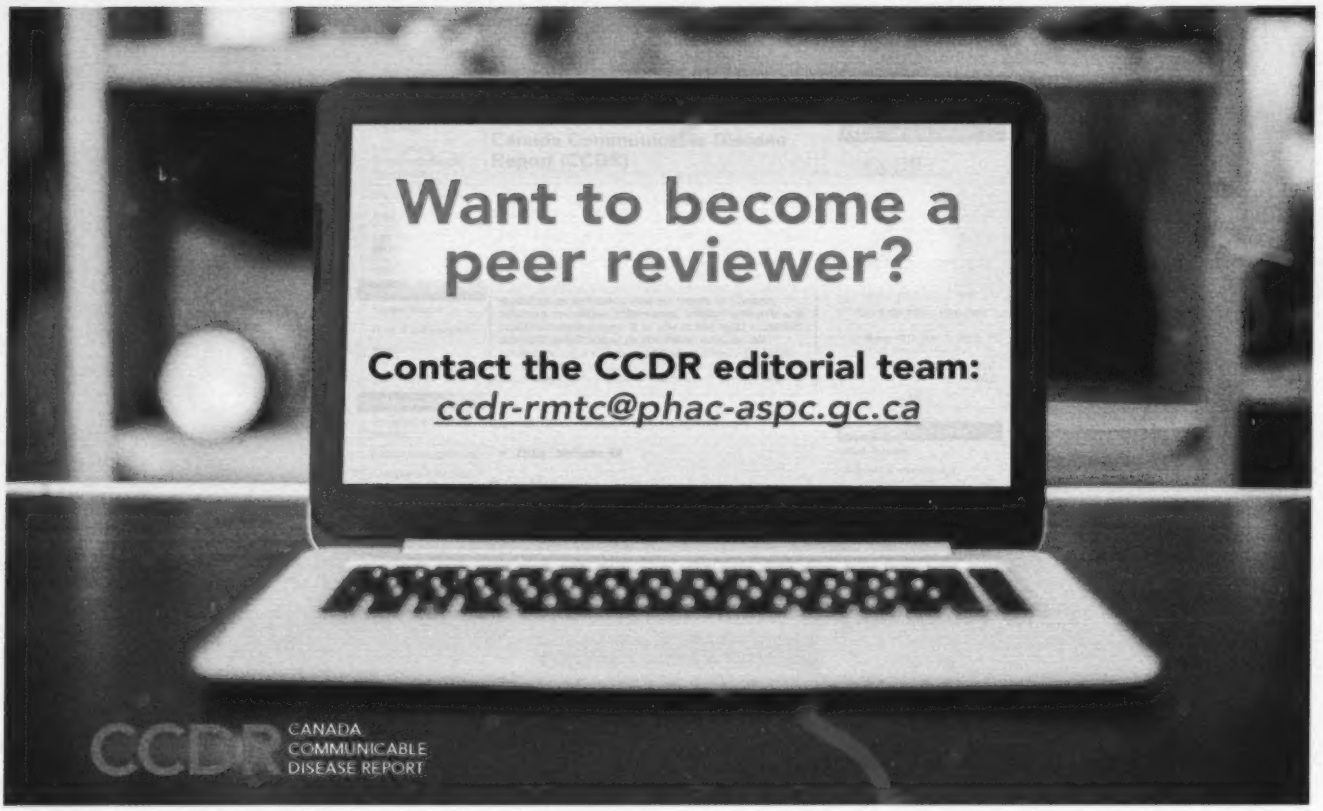

SURVEILLANCE

Assessing vaccine safety within Ontario's Universal Influenza Immunization Program, 2012-2013 to 2014-2015

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Abstract

Background: Influenza vaccine is recommended to prevent influenza-related morbidity and mortality. Post-marketing surveillance of adverse events following influenza vaccine is essential to monitor vaccine safety, inform immunization program planning and evaluation, and build confidence in immunization.

Objective: To summarize adverse events following immunization (AEFIs) reported after receipt of influenza vaccines administered within the Universal Influenza Immunization Program in Ontario.

Methods: AEFIs following administration of influenza vaccines between September 1, 2012 and August 31, 2015 were extracted from the Integrated Public Health Information System (iPHIS) on September 1, 2015. Events were grouped by provincial surveillance definitions. Reporting rates were calculated using provincial population estimates or net doses distributed as the denominator. The standard World Health Organization definition of serious AEFIs was used.

Results: There were 12.1 million doses of influenza vaccine distributed in Ontario and 528 AEFIs reported following influenza vaccines administered over three seasons. The annualized reporting rate was 4.4 per 100,000 doses distributed with a significant decreasing trend over time ($p<0.05$). The median age was 39.6 years (range six months–96 years); children under four years of age had the highest reporting rate (3.5 per 100,000 population). Disproportionate reporting among females was observed (76.5 percent), most notably in those 18 years and older. The most frequently reported events were injection site reactions (36.2 percent of reports). Others included allergic skin reactions (21.1 percent) and rashes (17.3 percent). Serious AEFIs were rare with a reporting rate of 1.6 per million doses distributed.

Conclusion: This assessment found a low rate of reported adverse events following influenza vaccines administered in Ontario. Most reported events were mild and resolved completely. The findings were consistent with the very good safety profile of influenza vaccines.

Suggested citation: Harris T, Wong K, Nair J, Fediurek J, Deeks SL. Assessing vaccine safety within Ontario's Universal Influenza Immunization Program, 2012-2013 to 2014-2015. Can Comm Dis Rep 2016;42:181-6.

Introduction

Influenza is a respiratory infection which causes approximately 12,200 hospitalizations and 3,500 deaths in Canada each year (1). Annual seasonal influenza vaccination is the most effective way to prevent influenza and its complications. There are multiple influenza vaccines authorized in Canada for use in individuals six months of age and older. Specific products include inactivated trivalent and quadrivalent vaccines (including adjuvanted and high-dose formulations) and live attenuated trivalent and quadrivalent vaccines with varying indications based on age and immune status (1,2). The National Advisory Committee on Immunization (NACI) recommends influenza vaccine to all individuals six months of age and older without contraindications, with particular focus on people at high risk of influenza-related complications or hospitalization and people capable of transmitting influenza to those at high risk (1). Ontario has had a publicly-funded Universal Influenza Immunization Program since 2000 (3). All Ontarians six months of age and older, who live, work or go to school in the Province are eligible for yearly publicly-funded influenza vaccine. Most influenza vaccines in the Province are administered within the Universal Influenza Immunization Program, however influenza vaccine products which are authorized for use but not included in the public program may be purchased privately.

Influenza vaccines are generally safe and well tolerated. For influenza vaccines administered by intramuscular injection, the most common side effect is pain at the injection site, which affects between 40 to 60 percent of healthy adults,

but is generally mild and resolves within a few days (4,5). Higher frequencies of injection site reactions are observed for adjuvanted and high-dose formulations. The occurrence of serious adverse events is rare and includes anaphylaxis and Guillain-Barré syndrome (GBS) (1). Post-marketing surveillance of influenza vaccines is essential to continue to demonstrate vaccine safety over time, to inform evaluation and build confidence in influenza immunization programs. Information from public health surveillance of adverse events following immunization (AEFIs) provides relevant and timely information to address concerns about vaccine safety, which have been shown to be a key barrier influencing vaccine acceptance among the general population (6-8) and health care workers (9-11).

Our objective is to summarize influenza AEFIs reported in Ontario during three recent influenza seasons to support a comprehensive evaluation of the Universal Influenza Immunization Program in Ontario.

Methods

Definitions

A confirmed AEFI is defined as "Any reported event in a vaccine recipient which follows immunization that cannot be clearly attributed to other causes. A causal relationship with the administration of the vaccine does not need to be proven" (12). Adverse events are defined according to event-specific provincial surveillance criteria (12). AEFIs are further defined as serious if they meet the World Health Organization standard definition which specifies that a serious AEFI is one that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (13,14). Other important medical events include: anaphylaxis, encephalitis, acute disseminated encephalomyelitis, myelitis, meningitis, GBS, acute cerebellar ataxia and thrombocytopenia. These events do not meet the above definition of serious and were measured and presented separately. Reports of events managed as anaphylaxis were further assessed using the Brighton Collaboration case definition and diagnostic levels of certainty (15).

In Ontario, reporting of AEFIs by specific health professionals (e.g., physicians, nurses and pharmacists) is mandated by provincial public health legislation (16); however, voluntary reporting from vaccine recipients or their caregivers also occurs. Reports of AEFIs are received by local public health units (PHUs) who investigate and enter information according to provincial surveillance guidelines into the Integrated Public Health Information System (iPHIS), the electronic reporting system for reportable diseases and AEFIs in Ontario.

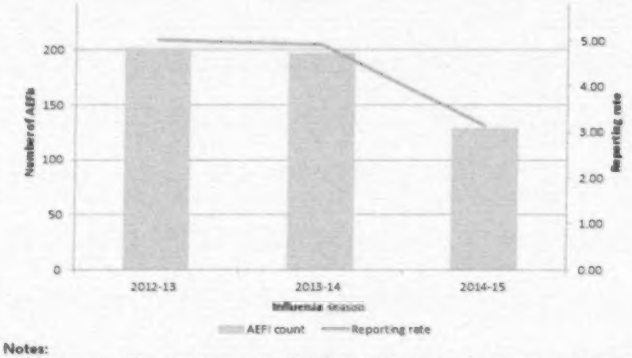
The review included all AEFIs reported following administration of influenza vaccines administered within the Universal Influenza Immunization Program between September 1, 2012 and August 31, 2015. Data was extracted from iPHIS on September 1, 2015. Vaccine products utilized within the Universal Influenza Immunization Program between 2012-2013 and 2014-2015 were trivalent inactivated vaccines including: Fluviral®, Agriflu®, Vaxigrip®, Fluzone® (2014-2015 only) and Fluad® (for 65 years and older who reside in long-term care facilities). Reports following administration of live attenuated influenza vaccine only were excluded, as they represented a very small number of reports (n=4) and were not part of the Universal Influenza Immunization Program during the reporting period.

Proportions were based on reports with completed data in iPHIS, therefore the denominator varies by variable. Temporal trends were assessed by influenza season, defined as September 1 to August 31 for the purposes of provincial influenza AEFI surveillance. AEFI reporting rates were calculated using both doses distributed and population-based denominators. Reporting rates were calculated over time and by event-type using net doses distributed within the publicly-funded program as the denominator. This was calculated based on estimates of net vaccine distribution data provided by the Ontario Government Pharmaceutical and Medical Supply Service which is adjusted for wasted or returned reusable vaccine. Reporting rates were calculated by demographic groups (e.g., age, sex and geography) using population-based denominators in the absence of information about dose distribution within these groups. Population denominators were based on 2012 and 2013 estimates for the 2012-2013 and 2013-2014 influenza seasons, respectively and 2014 projection for the 2014-2015 season (17,18). A statistical analysis was performed using SAS version 9.3 and Microsoft Excel 2010. Trends in incidence rate over the entire study period were assessed using Poisson regression and *p*-values less than 0.05 were considered statistically significant. This project was approved by the Public Health Ontario Ethics Review Board.

Results

There were 528 AEFIs reported following influenza vaccines administered within the Universal Influenza Immunization Program in Ontario between September 1, 2012 and August 31, 2015. During this time period, over 12.1 million net doses of Universal Influenza Immunization Program vaccine were distributed, for an annualized reporting rate of 4.4 per 100,000 doses distributed. A significant decreasing trend in the reporting rate by season was observed, with a marked drop in the reporting rate in 2014-2015, compared to 2012-2013 and 2013-2014 ($p<0.05$) (**Figure 1**).

Figure 1: Number of influenza AEFIs and reporting rate (per 100,000 doses distributed) in Ontario, 2012-2013 to 2014-2015



Notes:
1. AEFI counts include reports following publicly funded influenza vaccine only (e.g. excluding live attenuated influenza vaccine AEFIs) and are accurate as of September 1, 2015
2. Reporting rate is calculated using the following denominator: net publicly funded influenza vaccine doses distributed by Ontario Government Pharmacy and Medical Supply Service (OGPMSS) between September 1, 2012 and August 31, 2015

Individuals with AEFIs ranged in age from six months to 96 years (median 39.6 years). Over half of all reports (58.2 percent) were in adults 18–64 years of age; however, the highest age-specific reporting rates were in children less than four years and five to nine years of age (3.5 and 2.8 per 100,000 population, respectively) **(Table 1)**. Reporting rates within age group decreased over the three seasons with significant decreases in children less than four and adults 50 to 64 years of age. Disproportionate reporting among females was observed (76.5 percent overall), particularly in adult age groups (93.3 and 86.5 percent in 18–49 and 50–64 year olds, respectively). The highest female-to-male reporting rate ratios were in adults 18–49 and 50–64 years of age (13.8 and 6.2, respectively). Geographically, reporting rates by PHU varied widely from zero to 9.9 per 100,000 population with no noted pattern.

Table 1: Number of influenza AEFIs, percent and reporting rate in Ontario, by age group, 2012-2013 to 2014-2015

Age Category (years)[1]	Count[2]	Percent of AEFIs[2]	Percent of population[3]	Reporting rate[4] (per 100,000 population)
<4	75	14.3	5.3	3.49
5-9	61	11.6	5.4	2.78
10-17	22	4.2	9.0	0.59
18-49	180	34.2	43.8	1.00
50-64	126	24.0	20.9	1.50
65-79	50	9.5	11.5	1.11
80+	12	2.3	4.2	0.72
Total	**526**	**100.0**	**100.0**	**1.29**

[1] Age = Date of influenza vaccine administration – date of birth
[2] Total AEFIs = 528 (Two AEFI reports excluded for unknown age)
[3] Using 2014–15 population projections (N=13,672,718)
[4] Reporting rate is calculated using the following denominators: 2012 population estimates for 2012–13, 2013 for 2013–14 and 2014 projections for 2014–15

Most adverse events were reported following administration of influenza vaccine only (93.6 percent; n=494); 34 reports involved co-administration with other vaccines, most commonly, pneumococcal polysaccharide 23-valent (Pneu-P-23) vaccine (n=15) and tetanus, diphtheria, acellular pertussis (Tdap) vaccine (n=7). The most frequently reported events were injection site reactions which were documented in 36.2 percent of all reports. Other frequently reported types of events included allergic skin reactions (21.1 percent) and rashes (17.3 percent) **(Table 2)**. The highest event-specific reporting rates were similar to reporting volume with the highest rates for pain, redness and swelling at the injection site, allergic skin reactions and rash (1.3, 0.9 and 0.8 per 100,000 doses distributed, respectively). Medically important events (n=27) included anaphylaxis (n=22), thrombocytopenia (n=1) and acute rhabdomyolosis (n=1) as well as three serious events described below. Reports of events managed as anaphylaxis ranged in age from four to 84 years, were predominantly (81.8 percent; n=18) female and none were classified as serious. Eight (36.4 percent) met the Brighton Collaboration anaphylaxis case definition (one level I, six level II, one level III) and the remaining 14 reports (63.6 percent) did not contain sufficient evidence to meet the definition. Based on events that met the Brighton definition, the reporting rate of anaphylaxis was 0.7 per one million doses distributed.

Table 2: Number, percent distribution and reporting rate of influenza vaccine AEFIs in Ontario, by adverse event category, 2012-2013 to 2014-2015

Adverse event type[1]	Adverse event[2]	Number of AEFI reports[3]	Reporting rate[4]	Percent of all AEFI reports[3]	Number of serious reports
Injection site reactions	**Totals**	**190**	**1.6**	**36.2**	**8**
	Cellulitis	30	0.2	5.7	6
	Infected abscess	2	< 0.1	0.4	1
	Nodule	4	< 0.1	0.8	0
	Pain/redness/swelling at the injection site[5]	**162**	**1.3**	**30.9**	**3**
	Pain/redness/swelling extending beyond nearest joint	40	0.3	7.6	1
	Pain/redness/swelling <4 days[5]	7	0.1	1.3	0
	Pain/redness/swelling ≥4 days	129	1.1	24.6	2
	Sterile abscess	2	< 0.1	0.4	0
Systemic reactions	**Totals**	**156**	**1.3**	**29.7**	**7**
	Adenopathy/ lymphadenopathy	10	0.1	1.9	0
	Arthritis/arthralgia	16	0.1	3	1
	Fever ≥ 38 °C in conjunction with another reportable event	42	0.3	8	6
	Hypotonic-hypo-responsive episode (HHE)	1	< 0.1	0.2	0
	Parotitis	1	< 0.1	0.2	0
	Persistent crying/ screaming	1	< 0.1	0.2	0
	Rash	91	0.8	17.3	1
	Severe vomiting/ diarrhea[6]	14	0.1	2.7	1
	Syncope with injury[7]	1	< 0.1	0.2	0
	Thrombocytopenia	1	< 0.1	0.2	0
Allergic events	**Totals**	**145**	**1.2**	**27.6**	**1**
	Allergic reaction – skin	111	0.9	21.1	1
	Allergic reaction – other[8]	6	< 0.1	1.1	0
	Event managed as anaphylaxis[9]	22	0.2	4.2	0
	Oculorespiratory syndrome (ORS)	11	0.1	2.1	0
Neurologic events	**Totals**	**32**	**0.3**	**6.1**	**8**
	Anaesthesia/ paraesthesia[6]	10	0.1	1.9	2
	Bell's palsy	4	< 0.1	0.8	0
	Convulsions/seizures	9	0.1	1.7	3
	Encephalopathy/ encephalitis	2	< 0.1	0.4	1
	Guillian-Barré syndrome (GBS)	3	< 0.1	0.6	2
	Paralysis other than Bell's palsy	4	< 0.1	0.8	0
Other severe/ unusual events	**Totals**	**105**	**0.9**	**20.0**	**8**

Table footnotes

[1] Adverse event categories represent groupings of specific types of adverse events and are not mutually exclusive. For category totals, reports with more than one specific event within a category are counted only once. Thus category totals will not be the sum to the total of specific adverse events overall or within a category

[2] Includes only those adverse events where the count was at least one

[3] Each AEFI report may contain one or more specific adverse events which are not mutually exclusive. Percentages will not sum to 100%. The denominator is the total number of confirmed AEFI reports between 2012–2013 and 2014–2015 influenza season. Three reports were associated with zero adverse events, thus was excluded from the total confirmed AEFI reports in this specific analysis (n=525)

[4] Reporting rates are calculated using total dose distributed between 2012-2013 and 2014-2015 influenza seasons

[5] Includes the values "Pain/redness or swelling lasting less than four days", "Allergic reaction – cardiovascular" and Allergic reaction – respiratory" which were discontinued in iPHIS on January 1, 2013

[6] These events were implemented as new values added to the "adverse event reaction(s)" field in iPHIS on Jan 1, 2013

There were 20 serious AEFI reports across all seasons, representing 3.8 percent of all AEFIs and a reporting rate of 1.6 per million doses distributed. The proportion of reports that were classified as serious by season steadily decreased (5.0, 3.6 and 2.3 percent for 2012-2013 to 2014-2015, respectively) as did the serious reporting rate (from 2.5 per million doses distributed in 2012-2013 to 1.8 and 0.7 per million doses distributed in 2013-2014 and 2014-2015, respectively). The age range of serious reports was one to 81 years with the greatest number of reports in older adults 50–64 and 65–79 years, as well as children one to four years of age (four reports each). Females accounted for 60 percent of serious reports. The most frequent type of event among serious AEFIs was cellulitis (requiring hospital admission for treatment with IV antibiotics) (n=6). Other serious events included seizures (n=2; one febrile in a child, one afebrile in an adult), anaesthesia/paraesthesia (n=2), GBS (n=3), bilateral panuveitis (n=2; one also diagnosed with GBS), encephalitis (n=1), chronic inflammatory demyelinating process (n=1), polymyalgia rheumatica (n=1), febrile rash illness (n=1), infective abscess (n=1) and one report of sudden onset of mobility limitation with spontaneous resolution. No deaths were reported.

Out of all AEFIs, the majority were reported by health care professionals (63.8 percent: 25.3 percent from physicians and 38.5 percent from other health professionals), followed by self-reports and reports by family members (12.1 percent, 8.2 percent, respectively). For those reports with health care utilization information completed, 68.2 percent (n=353) sought outpatient medical consultation, 23.1 percent (n=121) were seen in the emergency department and 3.9 percent (n=20) were hospitalized. In most cases, the individual was recovered at the time of reporting (70.0 percent, n=336), 26.0 percent were not yet recovered (but full recovery was expected) and 4.0 percent (n=19) were documented as having residual effects. Among all reports, two were noted as being pregnant; both were mild, non-serious events which resolved completely. There were six AEFI reports where an immunization error was noted. All involved incorrect injection technique (e.g., intramuscular injection administered too high, needle length too short) resulting in prolonged pain at the injection site and one serious report of cellulitis.

Discussion

This assessment of adverse events following influenza immunization reported in Ontario during three recent influenza seasons is consistent with the well-established safety profile of influenza vaccines. Ontario's influenza AEFI reporting rate of 4.4 per 100,000 doses distributed between the 2012-2013 and 2014-2015 seasons represents one of the lowest vaccine-specific reporting rates of all publicly-funded vaccines in the Province (19). This rate was also lower than the most recently reported national influenza AEFI reporting rate (8.9 per 100,000 doses distributed; 2012-2013 to 2014-2015) (20) suggesting under-reporting in Ontario compared to other Canadian jurisdictions.

The decrease in reporting rate observed in 2014-2015 compared to previous years was unexpected and not fully understood. It was however, consistent with a decrease observed nationally during the same season. Some of the decrease could have been due to changes in provincial AEFI case definitions, which occurred during the first season in 2013 (e.g., limiting reporting of events involving pain, redness or swelling at the injection site to those that persist for four days or longer). Delayed reporting may play a role although in Ontario the proportion of late reports (e.g., reported after August 31) for 2012-2013 and 2013-2014 was minimal (3.5 and 1.5 percent, respectively) and a similar proportion of delayed reports for the 2014-2015 season would still result in a lower AEFI rate.

Age group-specific population-based reporting rates of influenza AEFIs were generally as expected with higher rates and proportions of AEFIs (compared to population distribution) in the youngest age groups. The observed female predominance in AEFI reporting has been previously noted in Ontario (21,22) and in other passive AEFI surveillance systems (23-25) although it appears particularly striking in this current assessment (93.3 and 86.5 percent in 18–49 and 50–64 year olds, respectively). The reasons for this phenomenon are likely multi-factorial. Differences in vaccine uptake between males and females may play a role, especially as health care workers (a target group for influenza vaccine) are more likely to be female. However, provincial estimates from the Canada Community Health Survey (12 years of age and older; influenza immunization, less than one year ago) suggest only a slight female predominance among those immunized (54.1 percent were female) (26). Other potential factors include: Differences between males and females in health care seeking behavior (27-29) once an AEFI occurs and different biologic response to vaccines (30,31). The difference in AEFI reporting by sex was less pronounced for serious AEFIs among which 60 percent were female.

Injection site reactions were the most frequently reported type of event in this assessment which is consistent with clinical trials and post-marketing surveillance of influenza vaccine products administered by intramuscular injection (4,5,23,32). Unlike the relatively high volume of injection site reactions among all AEFIs, the rate of reporting was quite low (1.6 per 100,000 doses distributed). While this rate likely underestimates the actual occurrence of localized reactions, some degree of under-reporting is expected for these events which are typically mild and resolve on their own. Allergic events were also frequently reported, most of which were allergic skin reactions which is consistent with previous AEFI assessments (19,20,23). A small number of allergic events were classified as an event managed as anaphylaxis. Based on reports that met the Brighton definition, the reporting rate of anaphylaxis was comparable, albeit slightly lower than the expected rate of anaphylaxis

following influenza vaccines which has been estimated at about one per million doses of vaccine (33,34).

As expected, serious events following influenza vaccine during this time period were rare and most often related to events known to be rarely reported following receipt of influenza vaccines. For example, GBS is a rare event which is consistently reported in post-marketing surveillance of influenza vaccines, including in Ontario where there were three reports of GBS following influenza vaccine over three years. While the evidence considering influenza vaccination and GBS is inadequate to accept or reject a causal association (35), the absolute risk of approximately one excess case per one million vaccines (36-38) is much lower than that associated with influenza disease (39,40). Of note, there were two reports of bilateral panuveitis during this time period which have been described in more detail by Manusow and colleagues (41). Panuveitis is a rare condition most often associated with infectious or inflammatory causes (42) although there is no known causal association with vaccines (43).

Limitations of this analysis include those which are inherent to many passive AEFI surveillance systems such as data quality, completeness and reporting bias (23,24). Under-reporting of AEFIs has been previously demonstrated to be more prominent in Ontario compared to other jurisdictions (19) and is again suggested here. Reporting rates were calculated using the total population or doses distributed as the denominator, both of which are proxies for doses administered in the absence of a provincial population-based immunization registry. Although doses distributed are widely used in analyses of passive AEFI surveillance systems (23,24), it can underestimate AEFI reporting rates if vaccine wastage is not well captured or understood. Trend analysis includes only three seasons therefore interpretation may be limited. Analyses of additional seasons over a longer time period will further inform ongoing assessment of trends in AEFI reporting.

Conclusion

This assessment found that influenza vaccines administered within the Universal Influenza Immunization Program in Ontario resulted in a low rate of reported adverse events. Most reported events were mild and resolved completely. No unexpected safety issues were identified. These findings are consistent with the very good safety profile of influenza vaccines used in Canada and internationally. Continued surveillance is important to monitor for safety signals and reporting trends over time, particularly with the introduction of new influenza vaccines and to maintain professional and public confidence in influenza vaccine safety. Further analysis is needed to understand the decreasing rate over time and under-reporting within the surveillance system to optimize AEFI surveillance data in Ontario.

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Conflict of interest

None.

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RAPID COMMUNICATION

Update regarding interim Canadian recommendations for the use of a fractional dose of yellow fever vaccine during a vaccine shortage

Yellow Fever Working Group on behalf of the Committee to Advise on Tropical Medicine and Travel (CATMAT)*

September 2016 update

The *Interim Canadian recommendations for the use of fractional dose of yellow fever vaccine during a vaccine shortage* (1) published in August 2016 were developed by the Committee to Advise on Tropical Medicine and Travel (CATMAT) to address the recent shortage of yellow fever vaccine supply. The licensed marketer of the yellow fever vaccine in Canada has taken measures to address the shortage and a normal supply of vaccines is now available to designated yellow fever vaccination centres. The interim recommendations (1) are only intended for use during a vaccine shortage and CATMAT no longer recommends the use of a fractional dose of the yellow fever vaccine. Please refer to the standard recommendations for yellow fever vaccination in the *Canadian Immunization Guide* (2) and in the CATMAT *Statement for Travellers and Yellow Fever* (3).

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Summary of the National Advisory Committee on Immunization (NACI) Statement on Seasonal Influenza Vaccine for 2016–2017

Gemmill I[1,2], Zhao L[3], and Cochrane L[3], on behalf of the National Advisory Committee on Immunization (NACI)[4,*]

Abstract

Background: Influenza is a respiratory infection caused primarily by influenza A and B viruses. Vaccination is the most effective way to prevent influenza and its complications. The National Advisory Committee on Immunization (NACI) provides recommendations regarding seasonal influenza vaccines annually to the Public Health Agency of Canada (the Agency).

Objective: To summarize the NACI recommendations regarding the use of seasonal influenza vaccines for the 2016-2017 influenza season.

Methods: Annual influenza vaccine recommendations are developed by NACI's Influenza Working Group for consideration and approval by NACI, based on NACI's evidence-based process for developing recommendations, and include a consideration of the burden of influenza illness and the target populations for vaccination; efficacy and effectiveness, immunogenicity and safety of influenza vaccines; vaccine schedules; and other aspects of influenza immunization. These recommendations are published annually on the Agency's website in the NACI Advisory Committee Statement: *Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine* (the Statement).

Results: The annual NACI seasonal influenza vaccine recommendations have been updated for the 2016-2017 influenza season to include adults with neurologic or neurodevelopment conditions among the groups for whom influenza vaccination is particularly recommended; to include the new high-dose, trivalent inactivated influenza vaccine for use in adults 65 years of age and older; to recommend that egg-allergic individuals may also be vaccinated against influenza using the low ovalbumin-containing live attenuated influenza vaccine (LAIV) licensed for use in Canada (NACI has previously recommended that egg-allergic individuals may be vaccinated using inactivated influenza vaccines); and to remove the preferential recommendation for the use of LAIV in children 2–17 years of age. Two addenda to the 2016-2017 Statement address these new LAIV recommendations.

Conclusion: NACI continues to recommend annual influenza vaccination for all individuals aged six months and older, with particular focus on people at high risk of influenza-related complications or hospitalization, people capable of transmitting influenza to those at high risk and others as indicated.

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Introduction

Influenza is ranked among the top 10 leading causes of death in Canada (1). Although the burden of influenza can vary from year to year, it is estimated that, in a given year, there are an average of 12,200 hospitalizations related to influenza (2) and approximately 3,500 deaths attributable to influenza (3). The National Advisory Committee on Immunization (NACI) provides recommendations regarding seasonal influenza vaccines annually to the Public Health Agency of Canada (the Agency). NACI recommendations for the use of seasonal influenza vaccine for the 2016-2017 influenza season is summarized below. Complete details can be found in the *Statement on Seasonal Influenza Vaccine for 2016-2017* (4), which includes the *Canadian Immunization Guide Chapter on Influenza* (Section II of the Statement) and in the two addenda to the Statement (5,6) published on the Agency's website.

Methods

In order to prepare the 2016-2017 seasonal influenza vaccine recommendations, NACI's Influenza Working Group (IWG) identified and reviewed evidence regarding adults with neurologic or neurodevelopment conditions as a risk group for complications of influenza; the new high-dose, trivalent inactivated influenza vaccine licensed for use in adults 65 years of age and older (Fluzone® High-Dose [Sanofi Pasteur]); the administration of live attenuated influenza vaccine (LAIV) in egg-allergic individuals; and vaccine effectiveness (VE) of LAIV and inactivated influenza vaccine. Following the review and analysis of this information, the IWG proposed updated recommendations for vaccine use to NACI, based on NACI's evidence-based process for developing recommendations (7). NACI critically appraised the available evidence and approved the specific recommendations brought forward. The evidence review regarding Fluzone® High-Dose is published separately (8). The rationale and relevant considerations for all the updated recommendations are included in the full Statement for 2016-2017 (4) and the two addenda to the 2016-2017 Statement on LAIV use (5,6).

Results

New for the 2016-2017 influenza season:

Adults with neurologic or neurodevelopment conditions

As of 2015-2016, children and adolescents with neurologic or neurodevelopment conditions, including seizure disorders, febrile seizures and isolated developmental delay, have been included in the high-risk group for whom influenza vaccine is particularly recommended. Based on preliminary review of the literature and expert opinion, and consistent with other countries' recommendations, **NACI now includes adults with neurologic or neurodevelopment conditions in the high-risk group for whom influenza vaccine is particularly recommended**. From the preliminary review, it was noted that the odds ratios for influenza complications in patients with neurologic conditions in comparison to those without in the reviewed studies ranged from 1.57 (pneumonia: 95% confidence interval [CI], 1.05 to 2.36) to 19.11 (intensive care unit admission: 95% CI, 3.92 to 93.22) and 22.2 (hospitalization: 95% CI, 2.6 to 186.0) (9-11). The conditions identified as risk factors in the studies reviewed include neuromuscular, neurovascular, neurodegenerative, neurodevelopmental conditions and seizure disorders.

The preliminary literature review findings, rationale, and updated NACI recommendation for the inclusion of adults with neurologic or neurodevelopment conditions are published in the 2016-2017 Statement (4).

New high-dose, trivalent inactivated influenza vaccine (Fluzone® High-Dose [Sanofi Pasteur])

Fluzone® High-Dose influenza vaccine has been approved for use in Canada in adults 65 years of age and older. Fluzone® High-Dose is a trivalent inactivated influenza vaccine (TIV) containing 60 µg of haemagglutinin (HA) per strain (compared to 15 µg HA per strain in a standard dose), administered as a 0.5 mL dose by intramuscular injection. Based on the available evidence, **NACI concludes that there is evidence that high-dose TIV should provide superior protection compared with standard-dose TIV for adults 65 years of age and older**. This superior relative protection compared to standard-dose TIV appears to increase with increasing age over 65 years. Considering the burden of disease associated with influenza A(H3N2) and the evidence of superior efficacy of high-dose TIV compared to standard-dose TIV, it appears that high-dose TIV would provide the greatest benefit to people 65 years of age and older.

A complete literature review of the Fluzone® High-Dose influenza vaccine for adults 65 years of age and older is published separately (8) and the full NACI rationale and recommendations on its use are published in the 2016-2017 Statement (4).

Administration of LAIV to egg-allergic individuals

The safety of LAIV in egg-allergic individuals has now been studied in more than 1,100 children and adolescents (2–18 years of age) in the United Kingdom and Canada (12-14). After careful review of recently published studies, **NACI concludes that egg-allergic individuals may be vaccinated against influenza using the low ovalbumin-containing LAIV licensed for use in Canada**. The full dose of LAIV may be used without prior vaccine skin test and in any settings where vaccines are routinely administered. LAIV also appears to be well tolerated in individuals with a history of stable asthma or recurrent wheeze; however, it remains contraindicated for individuals with severe asthma (defined as currently on oral or high-dose inhaled glucocorticosteroids or active wheezing) or for those with medically-attended wheezing in the seven days prior to immunization.

The literature review on the safety of LAIV in egg-allergic individuals and updated NACI recommendation on the administration of LAIV to egg-allergic individuals are published in an Addendum to the 2016-2017 Statement (5).

Updated NACI recommendations for the use of LAIV in children 2–17 years of age

After careful review of available studies from the last several influenza seasons, NACI concludes that the current evidence is consistent with LAIV's providing comparable protection against influenza to that afforded by inactivated influenza vaccine in various jurisdictions and has revised its recommendations on the use of influenza vaccine in children 2–17 years of age:

1. **In children without contraindications to the vaccine, any of the following vaccines can be used: quadrivalent LAIV, quadrivalent inactivated influenza vaccine (QIV) or TIV.**

2. **The current evidence does not support a recommendation for the preferential use of LAIV in children and adolescents 2–17 years of age.**

Given the burden of influenza B disease in children and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine, NACI continues to recommend that a quadrivalent formulation of influenza vaccine be used in children and adolescents 2–17 years of age. If a quadrivalent vaccine is not available, TIV should be used.

The observational study data reviewed highlight the challenge in interpreting the VE of LAIV and inactivated influenza vaccine when point estimates by influenza subtype are derived based on small sample sizes associated with wide confidence intervals. Therefore, in making its recommendation, NACI recognizes the need to continue to monitor the data on the VE of LAIV closely by influenza subtype and the relative effectiveness of LAIV compared to inactivated influenza vaccine. NACI has identified the need for further research to address current knowledge gaps:

3. **NACI strongly encourages further multidisciplinary (e.g., epidemiology, immunology, virology) research to investigate the reasons for the discordant 2015-2016 VE estimates between studies and explanations for poor LAIV effectiveness against A(H1N1)pdm09 reported in some studies.**

4. **NACI strongly recommends that sufficient resources be provided to enhance influenza-related research and sentinel surveillance systems in Canada to improve the evaluation of influenza vaccine efficacy and effectiveness to provide the best possible evidence for Canadian influenza vaccination programs and recommendations.**

Further details and rationale in support of the updated NACI recommendations on the use of LAIV in children 2–17 years of age are published in an Addendum to the 2016-2017 Statement (6).

Summary of NACI recommendations for the use of influenza vaccines for the 2016-2017 influenza season

NACI continues to recommend influenza vaccination for all individuals aged six months and older, with particular focus on people at high risk of influenza-related complications or hospitalization, people capable of transmitting influenza to those at high risk and others as indicated in **Table 1**.

Table 1: Groups for whom influenza vaccination is particularly recommended[1]

People at high risk of influenza-related complications or hospitalization

- All pregnant women[2].
- Adults and children with the following chronic health conditions:
  - cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis and asthma),
  - diabetes mellitus and other metabolic diseases,
  - cancer, immune compromising conditions (due to underlying disease, therapy or both),
  - renal disease,
  - anemia or hemoglobinopathy,
  - **neurologic or neurodevelopment conditions**[3],
  - morbid obesity (body mass index [BMI] of 40 and over), and
  - children and adolescents (age six months to 18 years) undergoing treatment for long periods with acetylsalicylic acid, because of the potential increase of Reye's syndrome associated with influenza.
- People of any age who are residents of nursing homes and other chronic care facilities.
- People 65 years of age and older.
- All children six to 59 months of age.
- Aboriginal Peoples.

People capable of transmitting influenza to those at high risk

- Health care and other care providers in facilities and community settings who, through their activities, are capable of transmitting influenza to those at high risk of influenza complications.
- Household contacts (adults and children) of individuals at high risk of influenza-related complications (whether or not the individual at high risk has been immunized):
  - household contacts of individuals at high risk, as listed in the section above,
  - household contacts of infants under six months of age as these infants are at high risk of complications from influenza but cannot receive influenza vaccine, and
  - members of a household expecting a newborn during the influenza season.
- Those providing regular child care to children 59 months of age and younger, whether in or out of the home.
- Those who provide services within closed or relatively closed settings to persons at high risk (e.g., crew on a ship).

Others

- People who provide essential community services.
- People in direct contact during culling operations with poultry infected with avian influenza.

[1] Updated recommendation noted in bold
[2] The risk of influenza-related hospitalization increases with length of gestation (i.e., it is higher in the third than in the second trimester)
[3] These include seizure disorders, febrile seizures and isolated developmental delay in children and neuromuscular, neurovascular, neurodegenerative, neurodevelopmental conditions and seizure disorders in adults, but exclude migraines and neuropsychiatric conditions without neurological conditions

Recommended influenza vaccine options by specific age and risk groups and dosage and route of administration by age are summarized in **Tables 2** and **3**, respectively.

Table 2: Choice of influenza vaccine for selected age and risk groups (for persons without a contraindication to the vaccine)[1]

Recipient by age group	Vaccine types available for use	Comments
Children 6–23 months of age	• TIV • QIV • ATIV	TIV, QIV and ATIV are authorized for this age group. NACI recommends that, given the burden of influenza B disease, QIV should be used. If QIV is not available, either unadjuvanted or adjuvanted TIV should be used.
Children 2–17 years of age	• TIV • QIV • Quadrivalent LAIV	**In children without contraindications to the vaccine, any of the following vaccines can be used: LAIV, QIV, or TIV.** **The current evidence does not support a recommendation for the preferential use of LAIV in children and adolescents 2–17 years of age.** Given the burden of influenza B disease in children and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine, NACI continues to recommend that a quadrivalent formulation of influenza vaccine be used in children and adolescents 2-17 years of age. If a quadrivalent vaccine is not available, TIV should be used. LAIV is not recommended for children with immune compromising conditions. LAIV, TIV or QIV can be used in children with chronic health conditions, including asthma that is not severe[2], and cystic fibrosis without immune suppression.
Adults 18–59 years of age	• TIV • QIV • Quadrivalent LAIV	TIV and QIV are the recommended products for adults with chronic health conditions. TIV and QIV, instead of LAIV, are recommended for health care workers. LAIV is not recommended for adults with immune compromising conditions.
Adults 60–64 years of age	• TIV • QIV	TIV and QIV are authorized for use in this age group.
Adults 65 years of age and older	• TIV • QIV • ATIV • High-dose TIV	**Given the burden of Influenza A(H3N2) disease and evidence of better efficacy in this age group, it is expected that high-dose TIV should provide superior protection compared with the standard-dose intramuscular vaccine for older adults.**
Pregnant women	• TIV • QIV	LAIV is not recommended because of the theoretical risk to the fetus from administering a live virus vaccine.

Abbreviations: ATIV, adjuvanted trivalent inactivated influenza vaccine; LAIV, live attenuated influenza vaccine (quadrivalent formulation); QIV, quadrivalent inactivated influenza vaccine; TIV, trivalent inactivated influenza vaccine
[1] Updated recommendations noted in bold
[2] An individual with severe asthma is defined as someone who is currently on oral or high-dose inhaled glucocorticosteriods, is active wheezing, or has had medically-attended wheezing in the seven days prior to vaccination

Table 3: Recommended influenza vaccine dosage and route, by age, for the 2016-2017 influenza season

Age group	TIV without adjuvant or QIV IM[1]	MF59-adjuvanted TIV (Fluad Pediatric™ or Fluad®) IM	LAIV (FluMist® Quadrivalent) IN	Number of doses required
6–23 months	0.5 mL[2]	0.25 mL	-	1 or 2[3]
2–8 years	0.5 mL	-	0.2 mL (0.1 mL per nostril)	1 or 2[3]
9–17 years	0.5 mL	-	0.2 mL (0.1 mL per nostril)	1
18–59 years	0.5 mL	-	0.2 mL (0.1 mL per nostril)	1
60–64 years	0.5 mL	-	-	1
65 years and older	0.5 mL	0.5 mL	-	1

Abbreviations: IM, intramuscular; IN, intranasal; LAIV, live attenuated influenza vaccine (quadrivalent formulation); QIV, quadrivalent inactivated influenza vaccine; TIV, trivalent inactivated influenza vaccine

[1] Influvac® 18 years and older, Fluviral® six months and older, Agriflu® six months and older, Vaxigrip® six months and older, Fluzone® six months and older, Fluzone® High-Dose 65 years and older, Flulaval® Tetra six months and older, Fluzone® Quadrivalent six months and older

[2] This information differs from the product monograph

[3] Children six months to less than nine years of age who have never received the seasonal influenza vaccine require two doses of influenza vaccine, with a minimum interval of four weeks between doses. Eligible children less than nine years of age who have properly received one or more doses of seasonal influenza vaccine in the past should receive one dose per influenza vaccination season thereafter

Conclusion

NACI continues to recommend annual influenza vaccination for all individuals aged six months and older (noting product-specific age indications and contraindications), with particular focus on people at high risk of influenza-related complications or hospitalization, including all pregnant women, people capable of transmitting influenza to those at high risk and others as indicated.

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Conflict of Interest

None.

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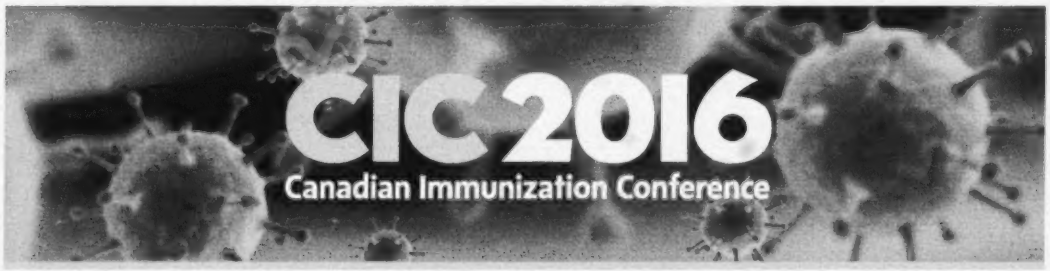

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Summary of the National Advisory Committee on Immunization (NACI) Statement Update on the Recommended Use of Hepatitis A Vaccine

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Abstract

Background: The severity of hepatitis A (HA) increases with age. Children less than six years of age are commonly asymptomatic or present with mild disease without jaundice and represent an important source of infection, particularly for household members and other close contacts. In older children and adults, HA is typically symptomatic. Older persons and individuals with chronic liver disease and immunocompromising conditions have an increased risk of progressing to fulminant hepatic failure resulting in death. Immunization with HA vaccine is recommended for pre-exposure immunization of persons at increased risk of infection or severe HA, as well as within 14 days of HA exposure for: susceptible household and close contacts of proven or suspected cases of HA; co-workers and clients of infected food handlers; and staff and attendees of group child care centres and kindergartens where HA has occurred. Canada's National Advisory Committee on Immunization (NACI) has previously recommended HA vaccination for persons one year of age and over.

Objectives: To make recommendations for the use of HA vaccine in infants less than one year of age and to clarify recommendations for the post-exposure use of human immune globulin (Ig).

Methods: The NACI Hepatitis Working Group (HWG) performed literature reviews and reviewed vaccine manufacturer provided data on the topic of HA post-exposure prophylaxis. All evidence was rated and reported in evidence tables. A knowledge synthesis was performed and NACI approved specific evidence-based recommendations, elucidating the rationale and relevant considerations.

Results: No studies on the efficacy or effectiveness of HA-containing vaccines in children six to less than 12 months of age were identified through the literature search. Receipt of two doses of HA-containing vaccines was found to be safe and immunogenic in infants six to 12 months of age. Limited data were available regarding HA-containing vaccine immunogenicity in adults over the age of 40 years.

Conclusion: There are now new NACI recommendations on HA vaccine and post-exposure use of Ig.

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Introduction

The severity of hepatitis A (HA) increases with age. Children less than six years of age are commonly asymptomatic or present with mild disease. In older children and adults, HA is typically symptomatic. Older persons and individuals with chronic liver disease and immunocompromising conditions have an increased risk of progressing to fulminant hepatic failure resulting in death. Immunization with HA vaccine is recommended for pre-exposure immunization of persons at increased risk of infection or severe HA, as well as within 14 days of HA exposure for: susceptible household and close contacts of proven or suspected cases of HA; co-workers and clients of infected food handlers; and staff and attendees of group child care centres and kindergartens where HA has occurred.

Canada's National Advisory Committee on Immunization (NACI) has previously recommended pre-exposure HA vaccination for persons one year of age and over. The NACI Hepatitis Working Group (HWG) has recently completed its work on the development of recommendations for the use of HA vaccine in infants less than one year of age and to clarify recommendations for the post-exposure use of human immune globulin (Ig). To do this it performed literature reviews and reviewed vaccine

manufacturer provided data on the topic of HA post-exposure prophylaxis. All evidence was rated and reported in evidence tables. A knowledge synthesis was performed and NACI approved specific evidence-based recommendations, elucidating the rationale and relevant considerations.

The review of the literature on the use of HA vaccine and current HA vaccine recommendations are published in the full NACI statement update (1) and the HA chapter of the *Canadian Immunization Guide* (2). In summary, no studies on the efficacy or effectiveness of HA-containing vaccines in children six to less than 12 months of age were identified through the literature search. Receipt of two doses of HA-containing vaccines was found to be safe and immunogenic in infants six to 12 months of age. Limited data were available regarding HA-containing vaccine immunogenicity in adults over the age of 40 years. The key recommendations are summarized below.

2016 NACI Recommendations on hepatitis A vaccine and post-exposure use of immunoglobulin

Recommendation 1: HA vaccine may be provided, beginning at six months of age, to infants who are at increased risk of infection or severe HA. (*NACI Recommendation Grade B*)

Infants at increased risk of severe HA infection may include those with an underlying liver disease of idiopathic, metabolic, infectious or cholestatic etiology. Canadian-born infants travelling to HA-endemic countries, including children of new Canadians returning to their country of origin to visit friends and relatives may be at increased risk of HA infection.

Recommendation 2: HA vaccine may be provided to infants beginning at six months of age, who are living in a household with an individual who is at increased risk of infection or severe HA. (*NACI Recommendation Grade B*)

Recommendation 3: For post-exposure prophylaxis, unless contraindicated or unavailable, HA vaccine is recommended in preference to Ig for healthy individuals six months of age and older. (*NACI Recommendation Grade B*)

Because the HA antibody content of Ig is assumed to decrease over time as a result of lower population-level antibody levels (due to lower rates of natural infection), and because of an excellent safety profile of inactivated HA-containing vaccine, immunization is preferred over the administration of a blood-derived product.

Recommendation 4: Immunization with HA vaccine may be considered for all individuals receiving repeated replacement of plasma-derived clotting factors. (*NACI Recommendation Grade I*)

The solvent-detergent (S/D) method used to prepare plasma-derived clotting factor concentrates does not reliably inactivate the HA virus. However, historically there has been no evidence of HA transmission from plasma-derived clotting factor in Canada and the risk of transfusion-related HA is extremely low because all pooled plasma is tested for HA. Due to a theoretical possibility of infection, immunization of individuals receiving large quantities of plasma-derived clotting factors may be considered. In Canada, product monographs of all S/D plasma-derived products used in the treatment of conditions requiring clotting factor substitution include recommendations for HA immunization.

Recommendation 5: For post-exposure prophylaxis within 14 days of exposure of susceptible adults 60 years of age and older who are household or close contacts of a case, Ig may be provided in addition to HA vaccine. (*NACI Recommendation Grade I*)

Individuals without a history of disease or previous immunization are susceptible to HA infection. Evidence is suggestive of reduced immunogenic response to HA vaccine, as well as of higher HA infection-related hospitalization and case fatality rates with increasing age. However, due to significant uncertainty about the incremental value of passive immunization on disease outcomes (including Ig HA antibody content), high HA antibody prevalence in older age groups and a small number of cases of HA infection-related complications in individuals over 60 years of age, the decision to include Ig for post-exposure HA prophylaxis should be made on a case-by-case basis. Given the lack of data to support benefit of Ig after 14 days, there is no recommendation for its use after this time period. Post-exposure prophylaxis with vaccine alone is recommended for outbreak response.

Recommendation 6: For post-exposure prophylaxis of susceptible individuals with chronic liver disease, Ig should be provided within 14 days of exposure in addition to HA vaccine. (*NACI Recommendation Grade B*)

Because of the risk of severe disease and a suboptimal immune response to HA vaccine among individuals who are immunocompromised and with chronic liver disease, Ig is recommended to provide immediate protection against HA infection until an active response to the vaccine is produced. Given the lack of data to support benefit of Ig after 14 days, there is no recommendation for its use after this time period.

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Conflict of interest

None.

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1. National Advisory Committee on Immunization (NACI). Update on the Recommended us of Hepatitis A Vaccine. Ottawa ON: PHAC; 2016. http://www.healthycanadians.gc.ca/publications/healthy-living-vie-saine/hepatitis-a-vaccine-update-recommended-use-2016-mise-a-jour-recommandations-hepatite-a-vaccin/index-eng.php
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Environmental Assessment for Investigational Use of *Aedes aegypti* OX513A

Source: Centre for Veterinary Medicine. Environmental Assessment for Investigational Use of *Aedes aegypti* OX513A. United States Food And Drug Administration. August 5, 2016. http://www.fda.gov/downloads/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/UCM514698.pdf (summary).

OX513A mosquitoes have been genetically engineered to encode a conditional or repressible lethality trait, which is a function of the overexpression of the tetracycline-repressible transactivator (tTAV) protein, and a red fluorescent marker protein (DsRed2). When tetracycline is not present (i.e., upon release of OX513A mosquitoes into the environment as in the proposed field trial), tTAV causes lethality in mosquitoes carrying at least one copy of the #OX513 recombinant DNA (rDNA) construct including the progeny of matings between OX513A males and wild-type females. The fluorescent marker can be used to identify the GE mosquitoes as larvae and pupae under laboratory conditions. More than 95% of OX513A progeny die before reaching viable adulthood if reared without tetracycline. Upon completion of the proposed trial, the population of *Ae. aegypti* is expected to be restored to its pre-field trial population level.

FDA's analysis in the Environmental Assessment is based on characterization of potential hazards and the likelihood of risk associated with investigational use of OX513A mosquitoes. Because risk is a function of hazard and exposure, if exposures are negligible, risk will also be negligible. These hazards and risks are described below, and FDA's findings drawn from that body of work form the basis of this finding of no significant impact (FONSI).

Toxic effects on humans or non-target animal health

Likelihood: extremely low. Risk: negligible.

- Almost all of the OX513A mosquitoes released as part of the proposed field trial will be male, and male mosquitoes do not bite humans or other animals.
- The trial protocol uses a sex sorting method based on the size difference between male and female pupae with quality control processes that ensure accuracy of sorting does not exceed a maximum of 0.2%.
- Thus, the overall probability of an OX513A female mosquito being released during the investigational trial is very low (0.2% at most) and the probability of this released female locating a human host and taking a blood meal is also low based on the estimated total human population in the trial area.

Allergenic effects on humans due to transfer of the rDNA construct to humans or non-target animals

Likelihood: extremely low. Risk: negligible.

- FDA determined that it is highly unlikely that the #OX513A rDNA construct could be transferred to humans or animals via biting because there is no known pathway for the naked, full length #OX513A rDNA to be present in mosquito saliva.
- If tTAV and DsRed2 proteins are expressed and secreted in saliva at all, these proteins are likely expressed below or close to the 1 ng range per Aedes female bite, which is much lower than the level at which known human allergens in mosquito saliva are expressed.

Increase in transmission of dengue or other diseases transmitted by mosquitoes

Likelihood: extremely low. Risk: negligible.

- OX513A male mosquitoes do not bite and, consequently, do not transmit diseases.
- A small number of females may be present at the site of the proposed release as a result of incomplete penetrance of the introduced lethality trait.
- Evidence suggests OX513A females have decreased vector competence because any OX513A females are expected to die in 2-3 days time, as the lack of tetracycline in the environment will turn on the lethality trait resulting in a lifespan too short to vector viral disease.

Increase in population of other mosquitoes that is opportunistic or via niche expansion that may contribute to the increase of disease

Likelihood: extremely low. Risk: negligible.

- the wild-type *Ae. aegypti* population would be expected to recover to pre-trial numbers after the cessation of OX513A mosquito releases.
- Therefore, the likelihood of adverse effects associated with an increase in the population of other mosquitoes that may contribute to the increase of diseases at the proposed trial site is extremely low.

Interbreeding with related mosquito species

Likelihood: extremely low. Risk: negligible.

- Mating in mosquitoes is very species specific.
- In the highly unlikely event that OX513A male mosquitoes do mate with other closely related mosquito species, it is highly unlikely that the rDNA construct would spread in the population of these mosquitoes due to the lethality phenotype conferred by this rDNA construct.

Adverse effects on predators, decomposers, or flora

Likelihood: Extremely low Risk: negligible.

- Because *Ae. Aegypti* breed in peri-domestic environments, they are subject to opportunistic predators that prey on their larvae and adults.
- FDA did not identify any specific parasitoid species associated with *Ae. aegypti*.
- In addition, no decomposers specific to *Ae. aegypti* were identified nor is a specific decomposer of detritus
- There are no reports indicating that *Ae. aegypti* mosquitoes are a pollinator for any plant species.

Development of resistance to insecticides

Likelihood: Extremely low Risk: negligible.

- Laboratory studies have shown that OX513A mosquitoes are susceptible to insecticides used for mosquito control.

Duration of Infant Protection Against Influenza Illness Conferred by Maternal Immunization: Secondary Analysis of a Randomized Clinical Trial

Source: Nunes MC, Cutland CL, Jones S, Hugo A, Madimabe R, Simões EA, Weinberg A, Madhi SA, Maternal Flu Trial Team. **Duration of Infant Protection Against Influenza Illness Conferred by Maternal Immunization: Secondary Analysis of a Randomized Clinical Trial**. JAMA Pediatr. 2016 Jul 5. doi: 10.1001/jamapediatrics.2016.0921. [Epub ahead of print]

Importance: Influenza immunization of women during pregnancy protects the young infants against influenza illness. The duration of this protection remains unclear.

Objective: To evaluate the duration of infant protection conferred by maternal immunization and its association with transplacental antibody transfer.

Design, Setting, and Participants: Infants born to women who participated in a randomized, double-blind, placebo-controlled clinical trial in 2011 and 2012 on the safety, immunogenicity, and efficacy of trivalent inactivated influenza vaccine (IIV3) during pregnancy were followed up during the first 6 months of life for polymerase chain reaction (PCR)-confirmed influenza illness. In a secondary analysis of a subset of infants, hemagglutination inhibition (HAI) antibodies were measured. The study was performed at a single center in South Africa. The secondary analysis was performed in October 2014.

Exposure: Maternal immunization for influenza.

Main Outcomes and Measures: The vaccine's efficacy against PCR-confirmed influenza illness and the percentage of infants with HAI titers of 1:40 or more by age group.

Results: There were 1026 infants (47.2% female) born to IIV3 recipients and 1023 infants (47.3% female) born to placebo recipients who were included in the analysis of the vaccine's efficacy. The vaccine's efficacy against PCR-confirmed influenza illness was highest among infants 8 weeks of age or younger at 85.6% (95% CI, 38.3%-98.4%) and decreased with increasing age to 25.5% (95% CI, -67.9% to 67.8%) among infants 8 to 16 weeks of age and to 30.3% (95% CI, -154.9% to 82.6%) among infants 16 to 24 weeks of age. Similarly, in the IIV3 group, the percentage of infants with HAI titers of 1:40 or more to the influenza vaccine strains decreased from more than 56% in the first week of life to less than 40% at 16 weeks of age and less than 10.0% at 24 weeks of age.

Conclusions and Relevance: Maternal immunization conferred protection against infection in the infants for a limited period during early life. The lack of protection beyond 8 weeks of age correlated with a decrease in maternally derived antibodies.

Trial Registration: clinicaltrials.gov Identifier: NCT01306669.

CCDR

CANADA COMMUNICABLE DISEASE REPORT

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